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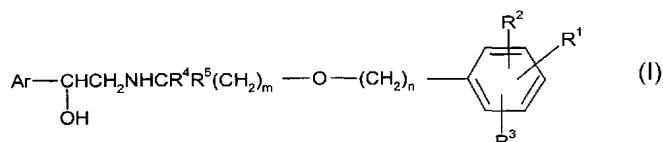
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(54) Title: PHENETHANOLAMINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF RESPIRATORY DISEASES



(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

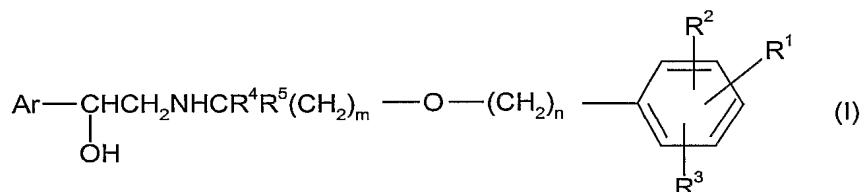
PHENETHANOLAMINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF RESPIRATORY DISEASES

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in
5 the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine
10 compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are
15 effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

20 According to the present invention, there is provided a compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

25

m is an integer of from 2 to 8;

n is an integer of from 3 to 11, preferably from 3 to 7;

with the proviso that m + n is 5 to 19, preferably 5 to 12;

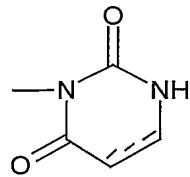
30 R^1 is $-\text{X}-\text{R}^6$; wherein

X is selected from $-(\text{CH}_2)_p-$ and C_{2-6} alkenylene;

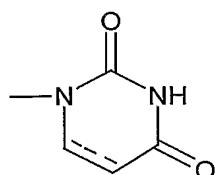
p is an integer from 0 to 6, preferably 0 to 4;

R^6 is selected from

5

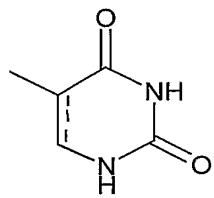


(a)

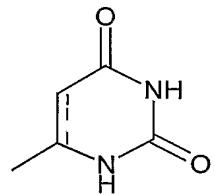


(b)

and



(c)



(d)

wherein — represents either a single or a double bond,

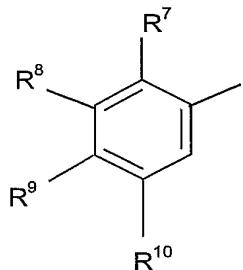
R^2 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo, and C_{1-6} haloalkyl;

10

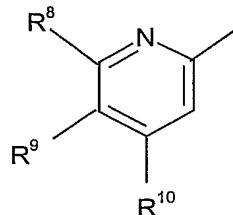
R^3 is selected from hydrogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo and C_{1-6} haloalkyl;

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that
15 the total number of carbon atoms in R^4 and R^5 is not more than 4, and

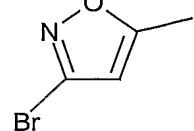
Ar is a group selected from



(e)

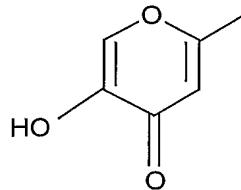


(f)



(g)

and



(h)

wherein R⁸ represents hydrogen, halogen, -(CH₂)_qOR¹¹, -NR¹¹C(O)R¹², -NR¹¹SO₂R¹²,

5 -SO₂NR¹¹R¹², -NR¹¹R¹², -OC(O)R¹³ or OC(O)NR¹¹R¹²,

and R⁷ represents hydrogen, halogen or C₁₋₄ alkyl;

or R⁸ represents -NHR¹⁴ and R⁷ and -NHR¹⁴ together form a 5- or 6- membered
10 heterocyclic ring;

R⁹ represents hydrogen, halogen, -OR¹¹ or -NR¹¹R¹²;

R¹⁰ represents hydrogen, halogen, haloC₁₋₄ alkyl, -OR¹¹, -NR¹¹R¹², -OC(O)R¹³ or
15 OC(O)NR¹¹R¹²;

R¹¹ and R¹² each independently represents hydrogen or C₁₋₄ alkyl, or in the groups

$-\text{NR}^{11}\text{R}^{12}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $-\text{OC(O)NR}^{11}\text{R}^{12}$, R^{11} and R^{12} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

5 R^{13} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4:

10

In a particular embodiment of this invention, in the group Ar , R^8 represents halogen, $-(\text{CH}_2)_q\text{OR}^{11}$, $-\text{NR}^{11}\text{C(O)R}^{12}$, $-\text{NR}^{11}\text{SO}_2\text{R}^{12}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{OC(O)R}^{13}$ or $\text{OC(O)NR}^{11}\text{R}^{12}$, and R^7 represents hydrogen or C_{1-4} alkyl;

15 or R^8 represents $-\text{NHR}^{14}$ and R^7 and $-\text{NHR}^{14}$ together form a 5- or 6- membered heterocyclic ring;

and all other substituents are as defined above.

20 In the compounds of formula (I) R^2 and R^3 preferably each represent hydrogen.

In the compounds of formula (I), R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

25 In the compounds of formula (I), m is suitably 3, 4, 5 or 6 and n is suitably 3, 4, 5 or 6. Preferably m is 5 and preferably n is 4 or 5, such that $\text{m} + \text{n}$ is 8, 9 or 10, preferably 9.

In the compounds of formula (I) the group R^6 preferably contains an unsaturated ring, that is, in each the moieties (a), (b), (c) and (d) ----- preferably represents a double bond.

30

In the definition of X , the term alkenylene includes both *cis* and *trans* structures. Examples of suitable alkenylene groups include $-\text{CH}=\text{CH}-$.

p is preferably zero.

35

In the compounds of formula (I) the group Ar is preferably selected from groups (e) and (f) above. In said groups (e) and (f), when R⁸ represents halogen this is preferably chlorine or fluorine. R¹¹ and R¹² preferably each independently represent hydrogen or methyl. R¹³ preferably represents substituted phenyl. The integer q preferably represents zero or 1.

5 Thus for example -(CH₂)_qOR¹¹ preferably represents OH or -CH₂OH;
 NR¹¹C(O)R¹² preferably represents -NHC(O)H;
 -SO₂NR¹¹R¹² preferably represents -SO₂NH₂ or SO₂NHCH₃;
 NR¹¹R¹² preferably represents -NH₂;
 -OC(O)R¹³ preferably represents substituted benzyloxy eg. OC(O)-C₆H₄-(_p-CH₃); and
 10 -OC(O)N R¹¹ R¹² preferably represents OC(O)N(CH₃)₂.

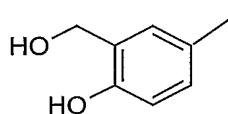
When R⁸ represents NHR¹⁴ and together with R⁷ forms a 5- or 6- membered heterocyclic ring -NHR¹⁴-R⁷- preferably represents a group:

-NH-CO-R¹⁵ where R¹⁵ is an alkyl, alkenyl or alkyloxy moiety;

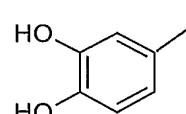
15 -NH-SO₂R¹⁶ where R¹⁶ is an alkyloxy moiety;
 -NH-R¹⁷- where R¹⁷ is an alkyl or alkenyl moiety optionally substituted by COOR¹⁸ where R¹⁸ is C₁₋₄ alkyl; or
 -NH-CO-S-;

wherein said alkyl, and alkenyl groups and moieties contain 1 or 2 carbon atoms.

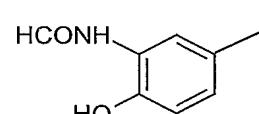
20 Particularly preferred groups (e) and (f) may be selected from the following groups (i) to (xxi):



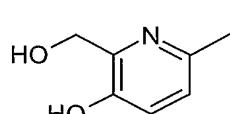
(i)



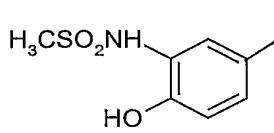
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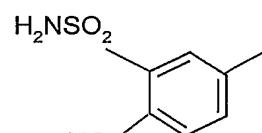
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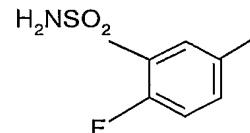
(iv)



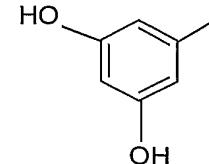
(v)



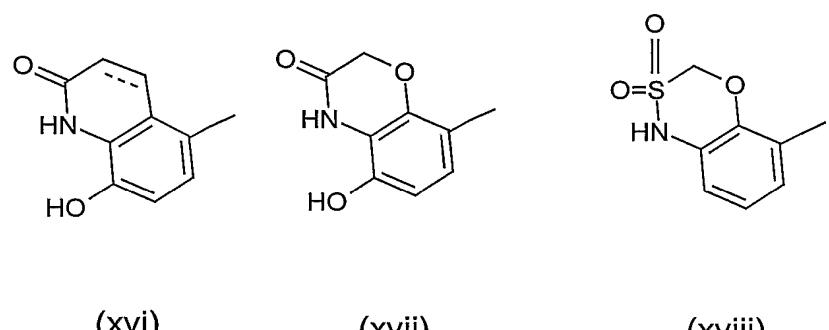
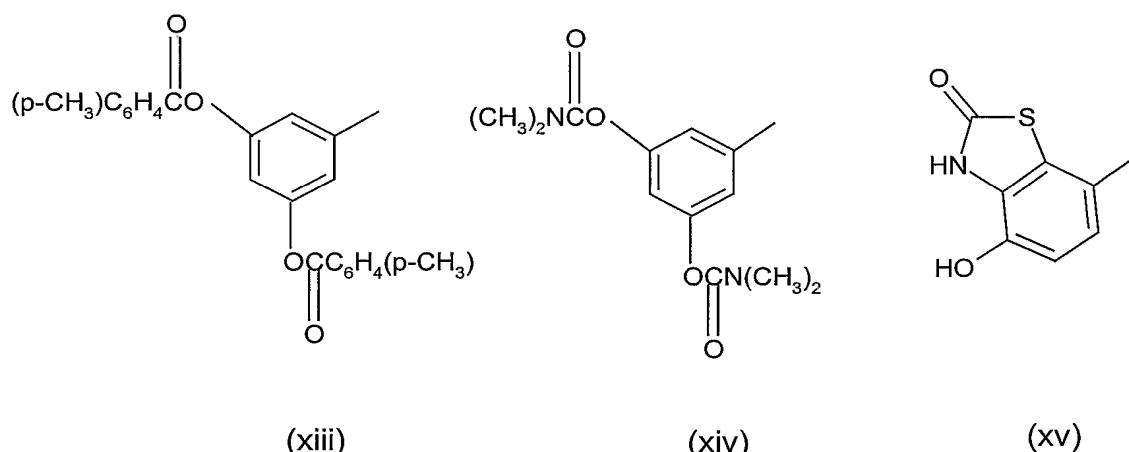
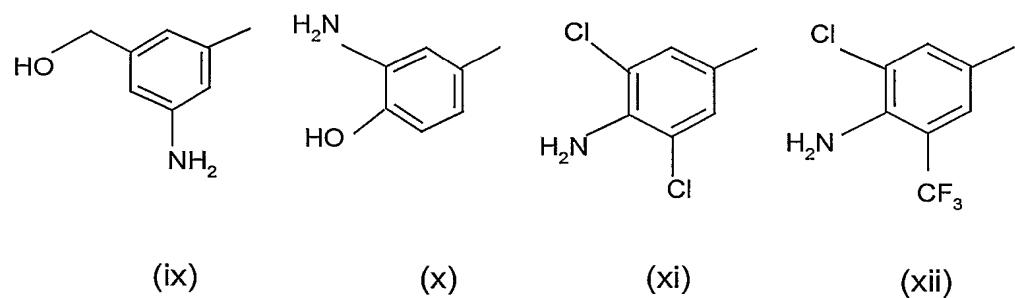
(vi)

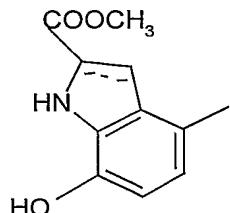


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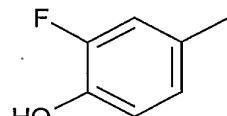


(viii)

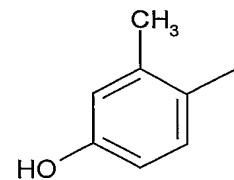




(xix)



(xx)



(xxi)

wherein the dotted line in (xvi) and (xix) denotes an optional double bond.

It is to be understood that the present invention covers all combinations of particular and

5 preferred groups described hereinabove.

Preferred compounds of the invention include:

10 1-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]pyrimidine-2,4(1H,3H)-dione;

15 3-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]dihydropyrimidine-2,4(1H,3H)-
dione;

20 5-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]pyrimidine-2,4(1H,3H)-dione;

25 3-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]pyrimidine-2,4(1H,3H)-dione;
5-((1R)-2-[(6-{4-[4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenyl]butoxy}hexyl)amino]-
1-hydroxyethyl]-2-hydroxyphenylformamide;

and salts, solvates and physiologically functional derivatives thereof.

The compounds of formula (I) include an asymmetric centre, namely the carbon atom of the



group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

5 Similarly, where R⁴ and R⁵ are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

10 Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

15 It will further be appreciated that the moieties (a), (b), (c) and (d) wherein — represents a double bond, may exist in tautomeric form, where one or both of the keto groups is converted to the enol form. The invention covers any and all tautomeric forms of compounds described herein.

20 Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or 25 associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

25 By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

30 Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, 35 naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or

halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

10 Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

As mentioned above, the compounds of formula (I) are selective β_2 -adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines 15 transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. As such, compounds of the invention may be suitable for once-daily administration.

20 Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways 25 obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

30 Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

35 Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or

physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the

5 present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

10

In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated.

15 In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

20

25 The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory,

allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or 5 physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is 10 generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

15 Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

20 Hereinafter, the term "active ingredient" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

25 The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of dry powder inhalers, metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient.

30 The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier (liquid, solid or gas) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with 35 carrier gas, such as air, liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in

5 an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory 10 ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the 15 powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile 20 injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose 25 containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, 30 be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (eg. lactose or starch). Use of lactose is preferred.

Each capsule or cartridge may generally contain between 20 μ g-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the 5 case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or metered in use (eg as in Turbuhaler, see EP 69715 or in the devices described in US 10 Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed 15 thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding 20 means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be 25 formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon 30 or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional 35 formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a

canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The

5 optimum particle size for inhalation into the bronchial system is usually 1-10 μm , preferably 2-5 μm . Particles having a size above 20 μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will
10 be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μm and not less than 15% will have a MMD of less than 15 μm .

15

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

20 Solutions for inhalation by nebulisation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

25 Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

30 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

35

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

5

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M₁, M₂, M₁/M₂ or M₃ receptor antagonist), other β₂-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β₂-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

20

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the

17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-

5 1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

10

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

20

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC₅₀ ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/57599 for another description of said assay.

5 The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred 10 compounds will have an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity.

15 A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC₅₀ ratio of about 0.1 or greater; said ratio is the ratio of the IC₅₀ value for competing with the binding of 1nM of [³H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC₅₀ value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μ M [³H]-cAMP as the substrate.

20 Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind 25 preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

Other compounds of interest include:

30 Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomast) and its salts, esters, pro-drugs or physical forms;

35 AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine

derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu

5 Cong Eur Resp Soc (Sept 19-23, Geneva) 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a phthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed
10 PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. *et al.* J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

15 Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and
20 M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

25 Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

30 Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

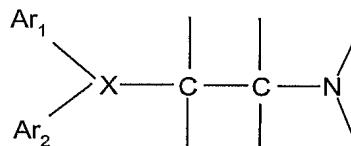
Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt - CAS-155-41-9.

35 Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-

139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, 5 CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoclopramide, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

10

Suitable antihistamines (also referred to as H_1 -receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1 -receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1 -receptors. The majority of these inhibitors, mostly first generation antagonists, have a 15 core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available:

20 ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine. Exemplary antagonists are 25 as follows:

Ethanolamines: carboxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripeleannamine HCl, and tripeleannamine citrate.

Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine.

30 Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in

5 combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

10 derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

derivative thereof together with a corticosteroid.

15

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

derivative thereof together with an anticholinergic.

20

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

derivative thereof together with an antihistamine.

25

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

derivative thereof together with a PDE4 inhibitor and a corticosteroid.

30

The invention thus provides, in a further aspect, a combination comprising a compound of

formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional

derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

35

The combinations referred to above may conveniently be presented for use in the form of

a pharmaceutical formulation and thus pharmaceutical formulations comprising a

combination as defined above together with a physiologically acceptable diluent or carrier

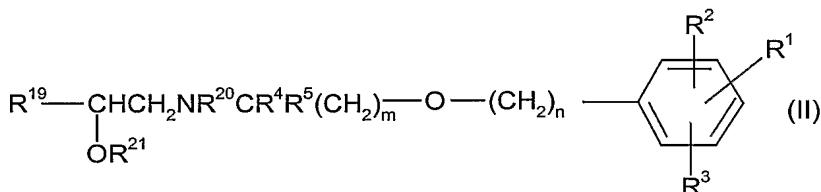
represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

5 According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a), (b), (c) or (d) as defined below, followed by the following steps in any order:

10 (i) optional removal of any protecting groups;
 (ii) optional separation of an enantiomer from a mixture of enantiomers;
 (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

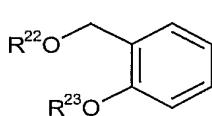
15 In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):



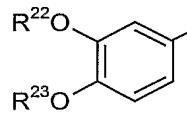
20 or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, m, and n are as defined for the compound of formula (I), R¹⁹ represents an optionally protected form of Ar; and R²⁰ and R²¹ are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group.

Protected forms of the preferred groups Ar may be selected from:

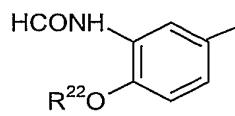
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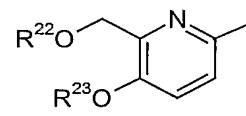
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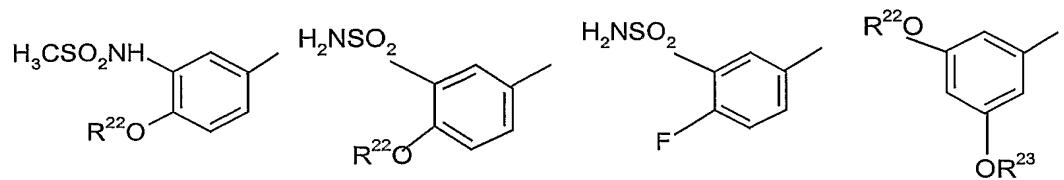
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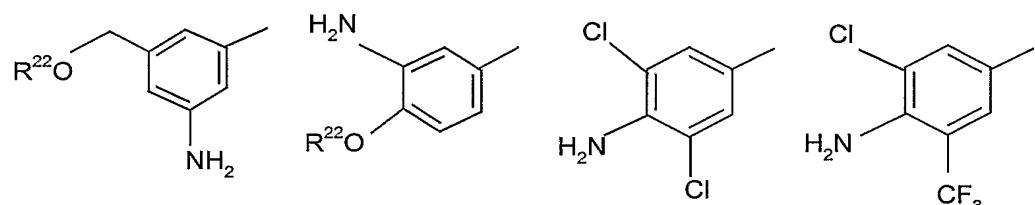
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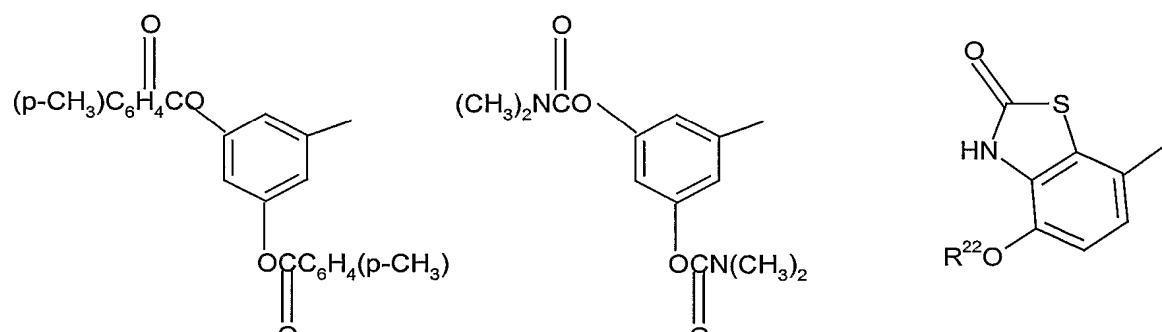


(ixa)

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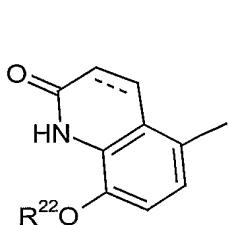


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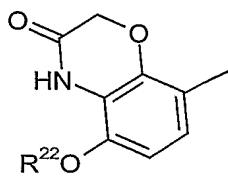
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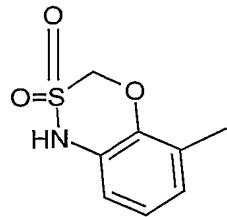
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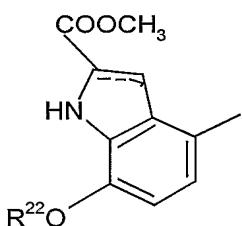
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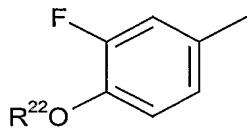
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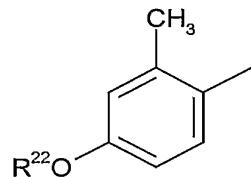
(xviiiia)



(xixa)



(xxa)



(xxia)

5

wherein R^{22} and R^{23} are each independently either hydrogen or a protecting group provided that at least one of R^{22} and R^{23} is a protecting group, and the dotted line in (xvia) and (xixa) denotes an optional double bond.

10

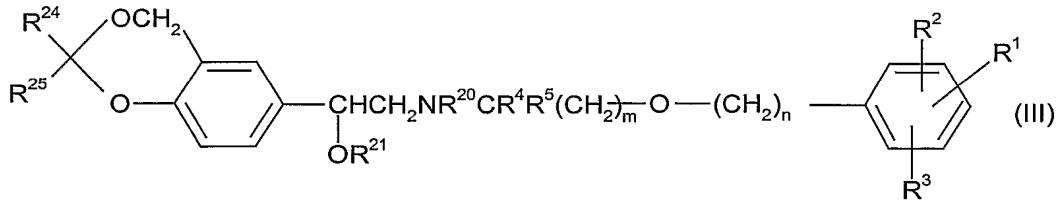
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R^{22} and R^{23} are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R^{20} include benzyl, α -methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the $-\text{CH}(\text{OH})$ group

5 may be orthogonally protected as $-\text{CH}(\text{OR}^{21})$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

10 The deprotection to yield a compound of formula (I), may be effected using conventional techniques. Thus, for example, when R^{22} , R^{23} , and/or R^{20} is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

15 When R^{22} and/or R^{23} is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^{20} may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a 20 particular embodiment of process (a), R^{22} and R^{23} may together represent a protecting group as in the compound of formula (III):



25 or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{20} , R^{21} , m , and n are as defined for the compound of formula (I), R^{24} and R^{25} are independently selected from hydrogen, C_{1-6} alkyl, or aryl or R^{24} and R^{25} together form a C_{3-7} cycloalkyl ring. In a preferred aspect, both R^{24} and R^{25} are methyl.

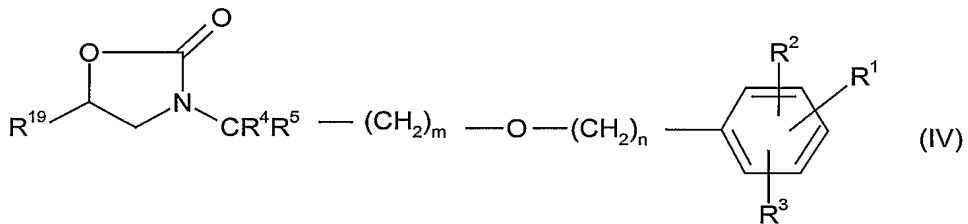
30 The compound of formula (III) may be converted to a compound of formula (I), by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketolisation in an alcohol, for example ethanol, in the presence

of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups R^{22} , R^{23} , R^{20} and R^{21} (including the cyclised protecting group formed by R^{22} and R^{23} as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when R^{22} and R^{23} together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the $CH(OH)$ moiety, followed by removal of R^{20} .

Depending on the nature of the group R^6 , some compounds of formulae (II) and (III) wherein R^{20} is hydrogen may be prepared from the corresponding compound of formula (IV):

15



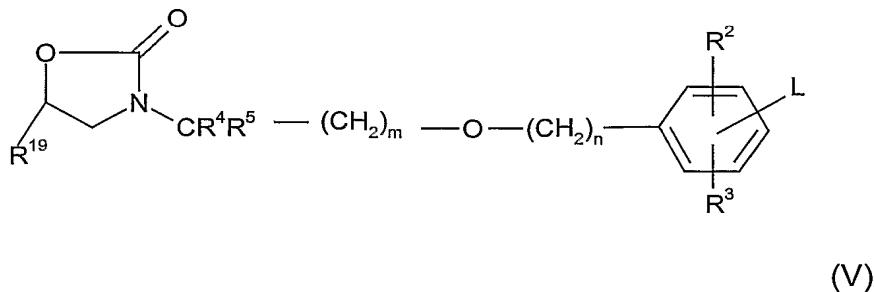
or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{19} , m , and n are as defined for the compound of formula (II) or (III).

20

In this process, the group R^6 should be chosen such that it is sufficiently stable to resist hydrolysis under the conditions required to open the oxazolidinone ring in the compound of formula (IV) to give a compound of formula (II) or (III).

25 The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

30 Compounds of formula (IV) may be prepared from the corresponding compound of formula (V):



5 or a salt or solvate thereof, wherein R², R³, R⁴, R⁵, R¹⁹, m and n are as defined for the compound of formula (II) and L is a leaving group group such as halo, eg. bromo or iodo, preferably iodo; or trifluoromethane sulfonate.

by coupling with a compound of formula (VI):

10



wherein X is as defined for formula (I), and R^{6a} represents R⁶, as defined for formula (I) or a derivative eg. a tautomeric and/or protected form thereof;

15

and A is a reactive group selected from boronic acid or an organo-zinc or organo-tin moiety;

20 The coupling of a compound of formula (V) with a compound of formula (VI) is conveniently effected in the presence of a catalyst system such as tetrakis(triphenylphosphine) palladium (0) with a base such as sodium carbonate, in a suitable solvent for example dimethoxyethane. When R^{6a} represents a protected derivative of R⁶, deprotection may be effected at any convenient stage of the synthesis, eg the final stage.

25

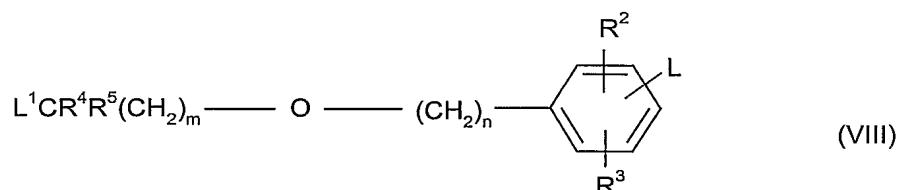
Compounds of formula (VI) are commercially available or may be prepared by methods well known to the person skilled in the art; (for example as described in Org. Prep. Proc. Int. 1998, 30, 433-437).

30 Compounds of formula (V) may be prepared by coupling a compound of formula (VII):



5

or a salt or solvate thereof, wherein R¹⁹ is defined for the compound of formula (V) with a compound of formula (VIII):



10

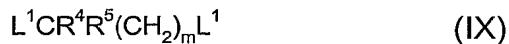
Wherein R¹, R², R⁴, R⁵, L, m and n are as defined for the compound of formula (V) and L¹ is a leaving group, for example a halo group, (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically methane sulphonate) an aryl sulphonate (typically toluenesulphonate) or a haloalkylsulphonate (typically trifluoromethane sulphonate).

15

The coupling of a compound of formula (VII) with a compound of formula (VIII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide or tetrahydrofuran.

20

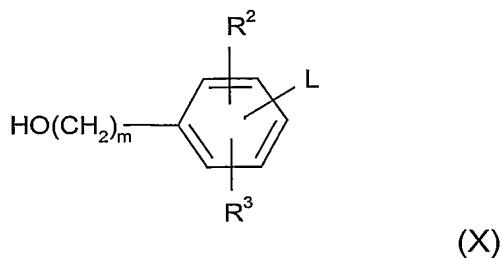
Compounds of formula (VIII) may be prepared from the corresponding dihaloalkane of formula (IX):



wherein R⁴, R⁵ and m are as defined for compounds of formula (I) and each L¹ represents

25 a halo, typically bromo;

by reaction with an alcohol of formula (X):

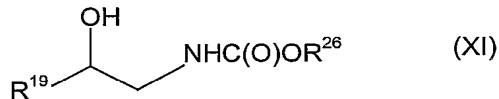


wherein R², R³, L and n are as defined for compounds of formula (VIII).

5 The coupling of compounds (IX) and (X) may be effected in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of a salt such as tetraalkylammonium bromide.

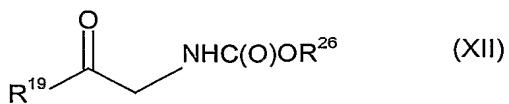
It will be appreciated that when the group L in compounds of formula (VIII) represents 10 bromo, this may, if desired, be exchanged for an iodo substituent by reaction with iodine in the presence of an alkyl lithium, such as n-butyl lithium, in a solvent such as tetrahydrofuran.

Compounds of formula (VII) may be prepared by ring closure of a compound of formula 15 (XI):



wherein R¹⁹ is defined for the compound of formula (VII) and R²⁶ is C₁₋₆alkyl, for example 20 tert-butyl, or aryl, for example phenyl. The ring closure may be effected by treatment with a base, such as a metal hydride, for example sodium hydride, in the presence of an aprotic solvent, for example, N,N-dimethylformamide.

Compounds of formula (XI) may be prepared from the corresponding ketone of formula 25 (XII):



wherein R^{19} and R^{26} are as defined for the compound of formula (XI), by reduction by any suitable method, for example by treatment with borane, in the presence of a chiral catalyst, such as CBS-oxazaborolidine, in a suitable solvent such as tetrahydrofuran.

5

The compound of formula (XII) may be prepared from the corresponding halide of formula (XIII):



wherein R^{19} is defined for the compound of formula (IV) and Y is a halo, suitably bromo.

10

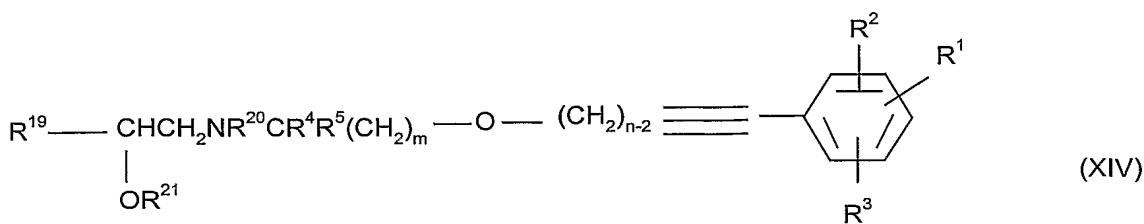
The conversion of a compound of formula (XIII) to a compound of formula (XII) may be effected by reaction with the protected amine $\text{HN}(\text{COOR}^{26})_2$ wherein R^{26} is as defined for the compound of formula (XII) in the presence of an inorganic base such as cesium carbonate, followed by selective removal of one of the COOR^{26} groups, for example by treatment with an acid such as trifluoroacetic acid.

15

Compounds of formula (XIII) may be prepared by conventional methods well known to those skilled in the art.

20 Compounds of formulae (I), (II) or (III) where R^{20} is hydrogen or a protecting group may be prepared according to the general methods described below.

In a further process (b) a compound of formula (I), (II) or (III) may be obtained by reduction of a compound of formula (XIV):



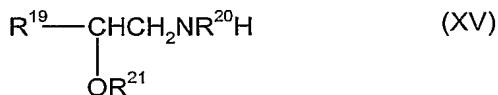
wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as defined for formula (I), R^{19} represents an optionally protected form of Ar and R^{20} and R^{21} each independently represent a hydrogen atom or a protecting group as defined for formula (II).

5

The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or platinum oxide.

It will be appreciated that where R^{19} is an unprotected form of Ar and R^{20} and R^{21} each represent hydrogen, the reduction will yield a compound of formula (I), but where one or more of R^{19} , R^{20} and R^{21} represent or contains a protecting group then reduction will yield a compound of formula (II) or (III), which may then be deprotected to give a compound of formula (I).

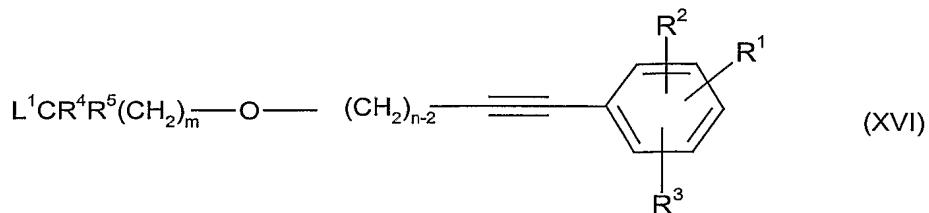
15 A compound of formula (XIV) may be prepared by reacting a compound of formula (XV):



wherein R^{19} , R^{20} , and R^{21} are as for formula (II),

20

with a compound of formula (XVI):



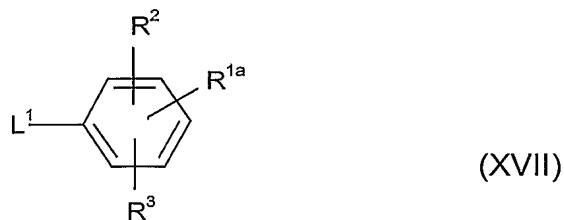
wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) and L^1 is as defined for the compound of formula (VIII).

The reaction of compounds of formulae (XV) and (XVI) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide.

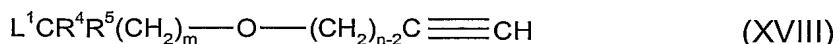
Compounds of formula (XV) are known in the art (for example EP-A 0947498) or may be readily prepared by a person skilled in the art, for example from the corresponding halide of formula (XIII) as defined above. The conversion of a compound of formula (XIII) to a compound of formula (XV) may be effected by reaction with sodium azide in a suitable solvent, for example N,N-dimethylformamide, to give the corresponding compound wherein Y denotes N_3 . The carbonyl group may then be reduced to the corresponding alcohol by any suitable method, for example by treatment with borane, in the presence of a chiral catalyst, such as (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole, in a suitable solvent such as tetrahydrofuran. The azide group may be reduced to the corresponding amine group by any suitable method, for example by catalytic hydrogenation in the presence of a catalyst such as palladium/charcoal or platinum oxide.

Further details concerning preparation of compounds (XV) wherein R^{19} is a group (iv) can be found in DE3524990; concerning the preparation of compounds (XV) wherein R^{19} is a group (i), (vii), and (xv) in EP-A-162576; concerning the preparation of compounds (XV) wherein R^{19} is a group (iii) in EP-A-22054; concerning the preparation of compounds (XV) wherein R^{19} is a group (x) in GB2165542 and concerning the preparation of compounds (XV) wherein R^{19} is a group (c) in GB2230523.

The compounds of formula (XVI) may be prepared by coupling a compound of formula (XVII):



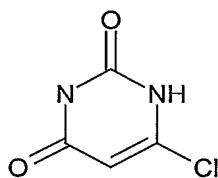
wherein R^2 , R^3 , and L^1 are as defined for formula (XVI); and R^{1a} represents $-X-R^{6b}$ wherein R^{6b} represents R^6 as hereinbefore defined or a precursor therefor; with a compound of formula (XVIII):



5

wherein R^4 , R^5 , m , n and L^1 are as defined for formula (XVI).

When R^{6b} represents a precursor for R^6 it may be for example a moiety of the formula:



10

which itself may be derived from the corresponding trione by reaction with phosphorous oxychloride. This moiety may be converted to a moiety R^6 at any convenient stage of the synthesis by hydrogenation, in the presence of a catalyst, for example palladium/charcoal or platinum oxide. Thus the chloro moiety may conveniently be retained during the 15 coupling of compound (XV) and (XVI) and then removed simultaneously with reduction of compound (XIV).

The coupling of a compound of formula (XVII) with a compound (XVIII) may be effected by in the presence of a catalyst system such as bis (triphenylphosphine) palladium dichloride 20 and copper (I) iodide with an organic base such as a trialkylamine, for example, diisopropylethylamine, in a suitable solvent, for example acetonitrile or N,N-dimethylformamide.

Compounds of formula (XVII) wherein R^1 represents a group XR^6 and R^6 represents a 25 group (a) may be prepared from the corresponding compound wherein R^6 represents NH_2 by reaction with a 3-isocyanatopropionate ester, e.g. the ethyl ester in a solvent such as dichloromethane, to give the R^6 precursor $NHC(O)NH(CH_2)_2C(O)OAlk$, which may be converted to the corresponding carboxylic acid by treatment with eg potassium trimethylsilanolate and an inorganic acid, eg sulphuric acid and effecting cyclisation by

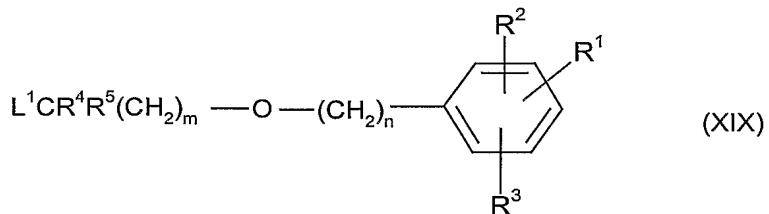
treatment with an activating agent such as di-t-butyl dicarbonate and a base such as dimethylaminopyridine.

Compounds of formula (XVII) wherein R⁶ represents a group (b) may be prepared from 5 the corresponding compound wherein R⁶ represents NH₂ by reaction with a cyanate salt, to form the corresponding phenylurea which is then treated with a dialkoxypropionate ester in the presence of sodium hydride and a solvent such as dioxane, followed by treatment with an organic acid such as aqueous acetic acid.

10 Compounds of formula (XVII) wherein R⁶ represents a group (c) may be prepared by methods analogous to the preparation of compounds (IV) described hereinabove.

In a further process (c) a compound of formula (I) , (II), or (III) may be obtained by alkylation of an amine of formula (XV) as hereinbefore defined

15 with a compound of formula (XIX):



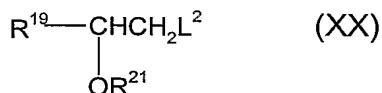
20 wherein R¹, R², R³, R⁴, R⁵, m, and n are as defined for the compound of formula (I) and L¹ is a leaving group as herein before defined for the compound of formula (VIII); followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II) and (III).

25 The compound of formula (I), may be formed directly when in the compound of formula (XV) R¹⁹ is Ar and R²¹ are each hydrogen, or via a compound of formula (II) or (III) which may or may not be isolated, when in the compound of formula (XV) at least one of R¹⁹, R²⁰ and R²¹ is or contains a protecting group.

30 The reaction of compounds of formulae (XV) and (XIX) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide, or acetonitrile.

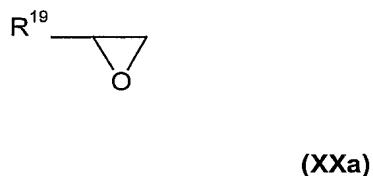
Compounds of formula (XIX) may be prepared in an analogous manner to compounds of formula (VIII), described hereinabove.

5 In a further process (d) a compound of formula (I), (II) or (III) may be prepared by reacting a compound of formula (XX):

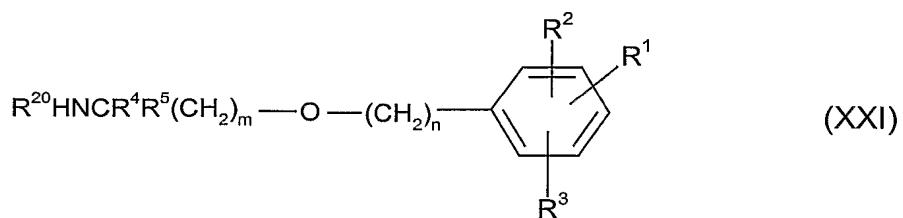


10

wherein R^{19} , and R^{21} are as hereinbefore defined and L^2 is a leaving group, or the corresponding epoxide of formula (XXa):



15 is reacted with an amine of formula (XI):



20 followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction may be effected using conventional conditions for such displacement reactions.

25 Compounds of formula (XX) and (XXa) may be prepared by methods known in the art.

Compounds of formula (XXI) may be prepared by reacting a compound of formula (XV) with an amine $R^{20}NH_2$.

5 It will be appreciated that in any of the routes (a) to (d) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by 10 subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating 15 suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional 20 conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I) for example: 25 compounds of formula (II), (III) and (IV) as defined above, or an optical isomer, a salt, or a protected derivative thereof.

For a better understanding of the invention, the following Examples are given by way of 30 illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:

LCMS: Liquid Chromatography Mass Spectrometry

35 MS : mass spectrum

TSP+ve : thermospray mass spectrum positive mode

HPLC: high pressure liquid chromatography

RT : retention time

THF : tetrahydofuran

DCM : dichloromethane

5 DMF : N,N-dimethylformamide

EtOAc : ethyl acetate

Et₂O : diethyl ether

EtOH : ethanol

MeOH : methanol

10 bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.

15 Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum.

20 These are commercially available from Varian.

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0% B,

25 0.7-4.2 min 100% B, 4.2-5.3 min 0% B, 5.3-5.5 min 0% B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Preparative mass directed HPLC was conducted on a Waters FractionLynx system comprising of a Waters 600 pump with extended pump heads, Waters 2700 autosampler, Waters 996 diode array and Gilson 202 fraction collector on a 10 cm X 2.54 cm ID ABZ+ column, eluting with 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), using the following elution gradient: 0.0-1.0 min 15% B, 1.0-10.0 min 55% B, 10.0-14.5 min 99% B, 14.5-14.9 min 99% B, 14.9-15.0 min 15% B at a flow rate 35 of 20 ml/min and detecting at 200-320 nm at room temperature. Mass spectra were recorded on Micromass ZMD mass spectrometer using electrospray positive and negative

mode, alternate scans. The software used was *MassLynx 3.5* with *OpenLynx* and *FractionLynx* options.

Example 1

1-[3-(4-[{6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino]hexyloxy]butyl]phenyl]pyrimidine-2,4(1H,3H)-dione

5 acetate

i) N-(3-Iodophenyl)urea

A suspension of sodium cyanate (6.5 g) in water (50 ml) was slowly added to a solution of 3-iodoaniline (6 ml) in 50% aqueous acetic acid (40 ml) and the mixture was stirred for 3 h
10 at 20 °C. Water was added and the solid was collected by filtration. The solid was washed with water, air-dried and triturated in diethyl ether to give *the title compound* (11.93 g). LCMS RT=2.76 min.

ii) 1-(3-Iodophenyl)pyrimidine-2,4(1H,3H)-dione

15 *N*-(3-Iodophenyl)urea (2.62 g) in dioxane (20 ml) was treated with sodium hydride (60% oil dispersion, 0.6 g) under nitrogen at 20 °C. After 1 h methyl dimethoxypropionate (2.22 g) was added and the mixture was stirred for 1 h at 20 °C and then heated to reflux for 2.5 h. The mixture was cooled to room temperature and then 40% aqueous acetic acid (100 ml) was added. The mixture was stirred overnight and the precipitated solid was
20 collected by filtration. The filtrate was extracted with DCM and combined with the solid obtained above to give *the title compound* (3 g) LCMS RT=2.46 min

iii) 6-Bromohexyl but-3-ynyl ether

25 3-Butyn-1-ol (42.4ml) was stirred vigorously with 1,6-dibromohexane (260ml) and tetrabutylammonium bisulphate (2.4g) in 50% aqueous sodium hydroxide solution (200ml) under nitrogen for 3 days. Water (ca 700ml) was added and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ (2 × 100ml) and the combined organic layers were washed with water, dried (MgSO₄) and concentrated. The residue in petroleum ether (bp 40 - 60°) was loaded onto a column of silica gel (1.5kg)
30 and the column was eluted with petroleum ether (bp 40 - 60°), then 10% diethyl ether in petroleum ether (bp 40 - 60°) to give *the title compound* (103.3g), δ (CDCl₃) 3.56(2H, t, J 7Hz), 3.47(2H, t, J 7Hz), 3.42(2H, t, J 7Hz), 2.45(2H, m), 1.99(1H, t, J 2Hz), 1.87(2H, m), 1.60(2H, m) and 1.50-1.33 (4H, m).

35 iv) 1-(3-[4-[(6-Bromohexyl)oxy]but-1-ynyl]phenyl]pyrimidine-2,4(1H,3H)-dione and 1-(3-[4-[(6-iodohexyl)oxy]but-1-ynyl]phenyl]pyrimidine-2,4(1H,3H)-dione

A mixture of 6-bromohexyl but-3-ynyl ether (3.49 g), 1-(3-iodophenyl)pyrimidine-2,4(1H,3H)-dione (3 g), copper (I) iodide (95 mg), bis(triphenylphosphine)palladium dichloride (350 mg) in DMF (13 ml) and diisopropylethylamine (4 ml) was stirred vigorously under nitrogen for 5 h. The solvents were removed under reduced pressure, 5 the residue was diluted with ethyl acetate and washed with aqueous hydrochloric acid, dilute aqueous ammonia solution, brine, dried (MgSO_4) and evaporated to dryness. The residue was purified by chromatography on Biotage (40 g cartridge) eluting with DCM, diethyl ether and EtOAc (500 ml each) to give *the title compounds* as a 2:1 mixture (2.12 g) LCMS RT=3.36 min and 3.47 min.

10

v) 2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone

2-Bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone (Glaxo DE 3513885, 1985) (52g) in DMF (300ml) was treated with sodium azide (12.24g) and the mixture was stirred for 2h at 20°C. The reaction mixture was diluted with EtOAc and washed with water and 15 dried (MgSO_4). The solvent was removed under reduced pressure to give *the title compound* (39.11g). TSP+ve 248(MH^+).

vi) (1R)-2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

(*R*)-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole solution in 20 toluene (1M, 7.5ml) was added to THF (75ml) and the solution was diluted to 0°C. Borane-THF complex (1M solution in THF, 125ml) was added and the mixture was stirred under nitrogen for 15min. A solution of 2-azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone (24.7g) in THF (250ml) was added dropwise over 1.5h at 5°C. The mixture was stirred for a further 1h and then cautiously treated with 2M HCl (100ml). The reaction 25 mixture was extracted with ether and the organic layer was washed with 2M HCl, NaHCO_3 , brine, dried (MgSO_4). The solvent was removed by evaporation and the residue was chromatographed on a Biotage column eluting with ether-petroleum ether(40-60°C) (1:9; 1:1) to give *the title compound* (16.99g). ES+ve 250 (MH^+).

30 vii) (1R)-2-Amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

(1*R*)-2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (16.99g) was hydrogenated over 10% Pd-C (1g) in EtOH (300ml). The catalyst was collected by filtration, and washed with EtOH. The combined washings were evaporated under reduced pressure and the residue was triturated in ether to give *the title compound* (5.86g). The mother liquors 35 were chromatographed on a Biotage column eluting with toluene:EtOH:aqueous ammonia

(85:14:1) to give a further batch of the *title compound* (5.99g). LCMS RT=1.68 min, ES+ve 206 (MH-H₂O)⁺.

viii) 1-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1H,3H)-dione

A mixture of (1*R*)-2-amino-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (1.67 g), 1-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1*H*,3*H*)-dione and 1-(3-{4-[(6-iodohexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (2:1; 2.1 g) was stirred in DMF (8 ml) for 18 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on Biotage (40 g cartridge) eluting with MeOH-DCM (1:19), followed by DCM-MeOH-aq. ammonia (95:5:1) to give *the title compound* LCMS RT=2.91 min.

ix) 1-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)pyrimidine-2,4(1H,3H)-dione

A solution of 1-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (1.22 g) in EtOAc (200 ml) and EtOH (100 ml) was hydrogenated over platinum oxide (400 mg) over 3 h. The catalyst was removed by filtration, washed with EtOAc and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on Biotage (40 g cartridge) eluting with aqueous ammonia-MeOH-DCM (1:4:95) and to give *the title compound* (470mg) LCMS RT=2.60 min

x) 1-[3-(4-[(6-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino}hexyl)oxy]butyl}phenyl)pyrimidine-2,4(1H,3H)-dione acetate

A solution of 1-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (470 mg) in acetic acid (20 ml) and water (8 ml) was heated to 76 °C for 40 min. The solvents were removed under reduced pressure and the residue was dissolved in MeOH and re-evaporated to give *the title compound*. (441mg) LCMS RT=2.30 min, ES+ve 526(MH)⁺.

Example 2

3-[3-(4-[(6-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino}hexyl)oxy]butyl}phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione acetate

i) Ethyl N-[(3-iodophenyl)amino]carbonyl}- β -alaninate

A solution of 3-iodoaniline (2.03 g) in DCM (20 ml) was treated with ethyl 3-isocyanatopropionate (2 g) at 0 °C and the mixture was stirred overnight. Ethanol (5 ml)

5 was added and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the residue was triturated in diethyl ether to give *the title compound* (1.85 g). LCMS RT=3.05 min

ii) N-[(3-Iodophenyl)amino]carbonyl}- β -alanine

10 A solution of ethyl *N*-[(3-iodophenyl)amino]carbonyl}- β -alaninate (1.84 g) in THF (20 ml) was treated with potassium trimethylsilanolate (1.3 g) at 20 °C and the mixture was stirred for 24 h. Dilute sulfuric acid was added and the solid was collected by filtration and dried to give *the title compound* (1.57 g) LCMS RT=2.83 min.

15 iii) 3-(3-Iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of *N*-[(3-iodophenyl)amino]carbonyl}- β -alanine (1.53 g) in THF (15 ml) and pyridine (0.5 ml) was treated with dimethylaminopyridine (61 mg) and di-*t*-butyldicarbonate (1.09 g). The mixture was stirred for 20 days at 20 °C, diluted with EtOAc, washed with dilute hydrochloric acid, brine, dried (MgSO₄) and evaporated to dryness to give *the title compound* (1.24 g) LCMS RT=3.20 min

iv) 3-(3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)dihydropyrimidine-2,4(1H,3H)-dione and 3-(3-{4-[(6-iodohexyl)oxy]but-1-ynyl}phenyl)dihydropyrimidine-2,4(1H,3H)-dione

Was prepared by methods similar to those described for Example 1 iv)

25 LCMS RT=3.23 min and 3.35 min

v) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)dihydropyrimidine-2,4(1H,3H)-dione

Was prepared by methods similar to those described for Example 1 viii)

30 LCMS RT=2.52 min.

vi) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)dihydropyrimidine-2,4(1H,3H)-dione

Was prepared by methods similar to those described for Example 1 ix)

35 LCMS RT=2.56 min.

vii) 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}butyl)phenyl]dihdropyrimidine-2,4(1H,3H)-dione acetate

5 Was prepared by methods similar to those described for Example 1 x)
LCMS RT=2.18 min, ES+ve 528 (MH)⁺.

Example 3

5-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

10 (hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}butyl)phenyl]pyrimidine-2,4(1H,3H)-dione

i) 6-Bromohexyl 4-(3-bromophenyl)butyl ether

A stirred mixture of 4-(3-bromophenyl) butan-1-ol (18 g) (EP 0 995 752A1), 1,6 dibromohexane (48 ml), tetrabutylammonium bromide (1.5 g) and 50% aqueous sodium 15 hydroxide solution (500 ml) was stirred for 2 days at ambient temperature. The mixture was poured into water (1000 ml) and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na₂SO₄) and evaporated. The residual oil was purified on the biotage eluting with light petroleum (40-60 °C), and then light petroleum (40-60 °C) - ether (9:1). The appropriate fractions were evaporated to give the *title compound* (18 g) 20 LCMS RT=4.34 min.

ii) 6-Bromohexyl 4-(3-iodophenyl)butyl ether

A solution of n-butyl lithium in hexane (1.6 M; 50 ml) was added to a stirred solution of 6-bromophenyl 4-(3-bromophenyl)butyl ether (21 g) in dry THF (150 ml) at -85 °C under 25 nitrogen. After 15 min a solution of iodine (19.8 g) in THF (100 ml) was added dropwise over 20 min. The solution was then allowed to warm up to 0 °C and aqueous sodium bisulphite was added. The mixture was poured into water and extracted into ether. The combined extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash silica gel column chromatography (1 kg) eluting with cyclohexane – ether (9:1). The 30 appropriate fractions were evaporated to give the *title compound* (17 g). LCMS RT=4.41 min.

iii) Di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate

Cesium carbonate (70.4g) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-35 4H-1,3-benzodioxin-6-yl)ethanone, (Glaxo, DE 3513885, 1985) (61.8g) and di-t-butyl iminodicarboxylate (47.15g) in acetonitrile (600ml) under nitrogen. After vigorous stirring

at 21° for 24 h the mixture was diluted with water (ca800ml) and the product was extracted with diethyl ether (1litre, then 200ml). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated to ca400ml. The white crystals were collected by filtration, washed with diethyl ether and dried to give the *title compound*

5 (24.4g) δ (CDCl_3) 7.78(1H, dd, J 8, 2Hz), 7.65 (1H, brs), 6.87(1H, d, J 8Hz), 4.97(2H, s), 4.88(2H, s), 1.56(6H, s) and 1.48 (18H, s) . Further concentration of the mother liquors gave additional product (13.8g). A third crop (7.1g) was obtained by chromatographing the mother liquors on silica gel, evaporating the appropriate eluate and triturating with diethyl ether.

10

iv) tert-Butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate

Trifluoroacetic acid (92ml) was added to a stirred solution of di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate, (352.55g) in dichloromethane (3.6litres) at 21° and the reaction was stirred for 1.5 h. Aqueous NaOH solution

15 (1.75litres) was added and after 10 min the phases were separated. The organic layer was washed with water, dried (MgSO_4) and evaporated to an oil. This was stored under high vacuum overnight and then triturated with hexane:ether (3:1) to give the crude product (226.61g). This was purified by recrystallisation from diethyl ether to give the *title compound* (122.78g). Further product (61.5g) was obtained from the mother liquors by 20 evaporation and chromatography on a Biotage using 15% ethyl acetate in hexane. LCMS RT = 3.37min.

v) tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate

A 2M solution of borane - dimethyl sulphide in THF (28ml) was added slowly to a 1M

25 solution of (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (56ml) at 0° under nitrogen. A solution of tert-butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate, (108.2g) in THF (1.3litres) was added slowly keeping the temperature below 5° followed by 2M solution of borane - dimethyl sulphide in THF (252ml) over 50 min. After 1 h, 2M HCl (170ml) was added with cooling and the 30 mixture was partitioned between ethyl acetate and water . The organic layer was washed with saturated NaHCO_3 solution and brine and dried (MgSO_4). The solution was concentrated and the product purified by chromatography on flash silica gel (800g), eluting successively with hexane:ethyl acetate (4:1 then 3:1) to give the *title compound* (93.3g), LCMS RT = 3.31min.

35

vi) (5*R*)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

tert-Butyl (2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate, (86.37g) in DMF (600ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 11.9g) in DMF (160ml) with cooling such that the internal temperature remained at 0° under nitrogen. The mixture was stirred at 21° for

5 2 h. The mixture was recooled to 0° and 2M HCl (134ml) was added. The mixture was diluted with water and the product was extracted with ethyl acetate twice. The solution was washed with brine twice, dried (MgSO_4) and evaporated to give the *title compound* (63.55g) LCMS RT = 2.66min.

10 vii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-[4-(3-iodophenyl)butoxy]hexyl]-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in oil 1.26 g) was added to a stirred, cooled (ice-bath) solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxazolidinone (5.47 g) in dry DMF (50 ml) under nitrogen and the mixture was stirred for 15 min at 5 °C. A solution of 15 6-bromohexyl 4-(3-iodophenyl)butyl ether (10.7 g) in DMF (30 ml) was then added dropwise over 10 min. The mixture was stirred for 2 h at ambient temperature, then poured into aqueous solution of ammonium chloride and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified on biotage (90 g cartridge) eluting with ether - hexane (3:2) to give the *title compound* (9.8 g). LCMS RT= 4.20 min.

20 viii) (5*R*)-3-(6-[4-[3-(2,4-Di-*tert*-butoxypyrimidin-5-yl)phenyl]butoxy]hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A stirred mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-[4-(3-25 iodophenyl)butoxy]hexyl]-1,3-oxazolidin-2-one (0.4g), 2,4-di-*tert*-butoxypyrimidin-5-yl boronic acid (0.158 g) and tetrakis(triphenylphosphine) palladium (0) (0.05 g) in dimethoxyethane (2 ml) and 1M sodium carbonate solution (2 ml) was heated at 80 °C for 1 h. The mixture was poured into water and extracted into ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified on 30 biotage (8 g cartridge) eluting with diethyl ether - cyclohexane (7:3) to give the *title compound* (0.34 g). LCMS RT= 4.36 min.

ix) (1*R*)-2-[(6-[4-[3-(2,4-Di-*tert*-butoxypyrimidin-5-yl)phenyl]butoxy]hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

35 A stirred solution of (5*R*)-3-(6-[4-[3-(2,4-di-*tert*-butoxypyrimidin-5-yl)phenyl]butoxy]hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.33 g) and potassium

trimethylsilanolate (0.3 g) in THF (5 ml) was heated at 80 °C for 3.5 h. The mixture was poured into a phosphate buffer solution (pH 5) and extracted into ethyl acetate. The extracts were washed with water, dried (Na₂SO₄). The solvent was removed *in-vacuo* to give *the title compound* (0.28 g). LCMS RT=3.50 min.

5

x) 5-[3-(4-[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]pyrimidine-2,4(1H,3H)-dione

A solution of (1*R*)-2-[(6-{4-[3-(2,4-di-*tert*-butoxypyrimidin-5-yl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (0.27 g) in acetic acid (4 ml) and water

10 (0.4 ml) was heated at 80 °C for 1.5 h. The solvent was removed *in vacuo* and the residue was purified on the biotage (90g) cartridge eluting with DCM-ethanol-aqueous-ammonia (100:8:1). The appropriate fractions were evaporated to give the *title compound* (0.105g). LCMS RT=2.31 min ES+ve 526 (MH)⁺

15 Example 4

3-[3-(4-[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]pyrimidine-2,4(1H,3H)-dione

acetate

20 i) 1-(3-iodophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

Sodium hydride (60% dispersion in oil, 1.00 g) was added to methanol (25 ml) at 0 °C. The mixture was allowed to stir for 30 min before the addition of diethyl malonate (3.5 ml) and *N*-(3-iodophenyl)urea (3.00 g). The reaction was heated at reflux for 18 h. The mixture was allowed to cool then poured into ice water and acidified with 2M HCl. The resultant precipitate was filtered, washed with water, and air dried giving *the title compound* (2.86 g). LCMS RT=2.53 min.

ii) 6-Chloro-3-(3-iodophenyl)pyrimidine-2,4(1*H*,3*H*)-dione

To a mixture of 1-(3-iodophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2.86 g) in phosphorous oxychloride (15 ml) was slowly added water dropwise. The reaction was heated at 60 °C for 20 h. The mixture was allowed to cool to room temperature and then phosphorous oxychloride removed under reduced pressure. The residue was poured into ice water and the resulting precipitate filtered and washed with water. The solid was added to saturated aqueous sodium hydrogen carbonate and the mixture stirred at room temperature for 18h. The suspension was filtered and the filtrate acidified with concentrated HCl to pH 1. The resulting solid was filtered, washed with water and purified

by chromatography on a Biotage cartridge (40 g) eluting with cyclohexane-ethyl acetate (3:2) to give *the title compound* (0.30 g). LCMS RT=2.63 min.

iii) 3-(3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)-6-chloropyrimidine-2,4(1H,3H)-dione

5 A mixture of 6-bromohexyl but-3-ynyl ether (1.15 g), 6-chloro-3-(3-iodophenyl)pyrimidine-2,4(1H,3H)-dione (0.3 g), copper (I) iodide (15 mg), bis(triphenylphosphine)palladium dichloride (90 mg), and diisopropylethylamine (2.5 ml) in DMF (7.5 ml) was stirred under nitrogen for 27 h. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with dilute aqueous ammonia solution, brine, dried 10 (MgSO₄) and evaporated to dryness. The residue was purified by chromatography on a Biotage cartridge (40g) eluting with cyclohexane-ethyl acetate (3:2) to give *the title compound* (0.16 g). LCMS RT=3.46 min.

iv) 6-Chloro-3-(3-{4-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-

15 hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1H,3H)-dione

A mixture of (1*R*)-2-amino-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (320mg), and 3-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (150 mg) were stirred in DMF (4 ml) for 18 h. The solvent was removed under reduced pressure and the residue was purified by silica SPE (10g cartridge) eluting with DCM-20 MeOH (99:1), followed by DCM-MeOH-aq. ammonia (95:4:1) to give *the title compound* (59mg). LCMS RT=2.56 min.

v) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)pyrimidine-2,4(1H,3H)-dione

25 A solution of 6-chloro-3-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (50 mg) in EtOH (15 ml) and 2M NaOH (2 ml) was hydrogenated over 10% Pd/C (40 mg) for 22 h. The catalyst was removed by filtration, washed with ethanol, and the filtrate removed under reduced pressure. The residue was diluted with water and neutralised with 1M HCl. 30 The aqueous phase was extracted with EtOAc, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by silica SPE (10g cartridge) eluting with DCM-MeOH (99:1), followed by DCM-MeOH-aq. ammonia (95:4:1) to give *the title compound* (30 mg). LCMS RT=2.47 min.

vi) 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino]hexyl]oxy]butyl]phenyl]pyrimidine-2,4(1H,3H)-dione acetate

A solution of 3-(3-{4-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-

5 hydroxyethyl]amino}hexyl)oxy]butyl]phenyl)pyrimidine-2,4(1H,3H)-dione (30 mg) in acetic acid (2 ml) and water (1 ml) was heated to 70 °C for 45 min. The solvents were removed under reduced pressure and the residue purified using mass directed HPLC. Removal of the solvent under reduced pressure produced *the title compound* after freeze drying from water and acetic acid (19 mg). LCMS RT=2.21 min, ES+ve 526 (MH)⁺.

10

Example 5

5-[(1R)-2-[(6-{4-[4-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl]-2-hydroxyphenylformamide acetate

15 i) 5-[(1R)-2-(Benzyl{6-[4-(3-iodophenyl)butoxy]hexyl}amino)-1-hydroxyethyl]-2-(benzyloxy)phenylformamide

A stirred mixture of 2-(benzyloxy)-5-[(2R)-oxiran-2-yl]phenylformamide (0.5g) and N-benzyl-N-{6-[4-(4-iodophenyl)butoxy]hexyl}amine (0.865g) were heated at 120° C for 3 h. The mixture was cooled and purified on a silica biotage cartridge (40g) eluting with ether - hexane (3:2). The appropriate fractions were evaporated to give *the title compound* (0.45 g). LCMS RT = 3.35 min.

ii) 5-[(1R)-2-[Benzyl(6-{4-[4-(2,6-di-*tert*-butoxypyrimidin-4-yl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl]-2-(benzyloxy)phenylformamide

25 A stirred mixture of 5-[(1R)-2-(benzyl{6-[4-(3-iodophenyl)butoxy]hexyl}amino)-1-hydroxyethyl]-2-(benzyloxy)phenylformamide (0.43 g), 2,4-di-*tert*-butoxypyrimidin-5-yl boronic acid (0.187 g) and tetrakis(triphenylphosphine) palladium (0) (0.1 g) in dimethoxyethane (5 ml) and 1M sodium carbonate solution (5ml) was heated at 85° C for 20 min. The mixture was poured into water (30 ml) and extracted into ethyl acetate (3 × 20 ml). The extracts were dried (Na₂SO₄) and evaporated. The residual oil was purified on a silica biotage cartridge (8 g) eluting with dichloromethane - ethanol – aqueous ammonia (100:8:1). The appropriate fractions were evaporated to give *the title compound* (0.24 g). LCMS RT = 3.60 min.

35 iii) 5-[(1R)-2-[(6-{4-[4-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)

phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-hydroxyphenylformamide acetate

A solution of 5-[(1*R*)-2-[benzyl(6-{4-[4-(2,6-ditert-butoxypyrimidin-4-yl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(benzyloxy)phenylformamide

(0.23 g) in ethanol (10 ml) was hydrogenated at 100 psi over a mixture of 10% palladium

5 on carbon (0.03 g) and Pearlman's catalyst (0.03 g) for 18 h. The catalyst was removed by filtration through celite and washed with ethanol. The filtrate and washings were evaporated to dryness under reduced pressure. The residual oil was heated in glacial acetic acid (5 ml) and water (1 ml) for 40 °C for 1 h. The solvent was evaporated to give a solid, which on trituration with diethyl ether gave *the title compound* (0.25 g). LCMS RT =

10 2.39 min, ES+ve 539 (MH⁺).

BIOLOGICAL ACTIVITY

15 In vitro measurements of compound potency and intrinsic activity at the human Beta 1, 2 and 3 receptor.

Method 1

20 The potencies of the compounds of Examples 2, 3, and 5 were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human 25 beta 2 adrenoreceptor, compounds of said examples had IC₅₀ values below 1 μM.

Method 2

30 Potency of compounds of the invention at the human beta 2, 1 and 3 receptors was also determined using Chinese hamster ovary cells co-expressing the human receptor with a reporter gene. Studies were performed using either whole cells or membranes derived from those cells.

35 The three beta-receptors are coupled via the Gs G-protein to cause a stimulation of adenylate cyclase resulting in increased levels of cAMP in the cell. For direct cAMP measurements either membranes or frozen cells have been used with either the HitHunter

enzyme fragment complementation kit (DiscoveRx) or the FP² fluorescence polarisation kit (Perkin Elmer) to quantify the levels of cAMP present. These assays provide a measure of agonist potency and intrinsic activity of the compounds at the various receptors.

5

The reporter gene in the cells has also been used to quantify potency at the beta 1 and 3 receptors. This is a reporter of cAMP levels using the cAMP response element upstream of a firefly luciferase gene. After stimulation of the receptor with an agonist an increase in the level of luciferase is measured as a quantification of the level of cAMP in the cell.

10

In this assay the potency of compounds at the human beta-2 receptor is expressed as a pEC₅₀ value. Compounds of Examples 1 and 4 had a pEC₅₀ of >6.

15

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

20

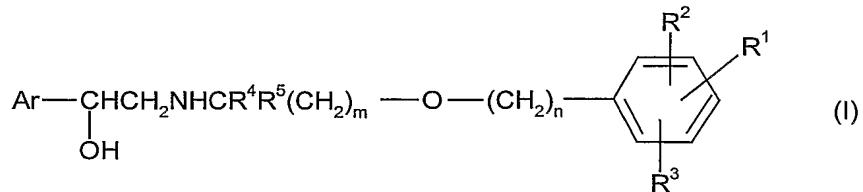
25

30

CLAIMS

1. A compound of formula (I)

5



or a salt, solvate or physiologically functional derivative thereof, wherein:

10 m is an integer of from 2 to 8;

n is an integer of from 3 to 11;

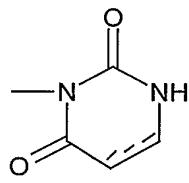
with the proviso that m + n is 5 to 19;

R¹ is -X-R⁶; wherein

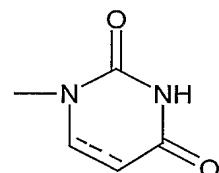
15

X is selected from -(CH₂)_p- and C₂₋₆alkenylene;

p is an integer from 0 to 6;

20 R⁶ is selected from

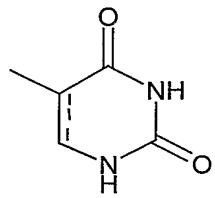
(a)



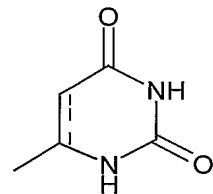
(b)

25

and



(c)



(d)

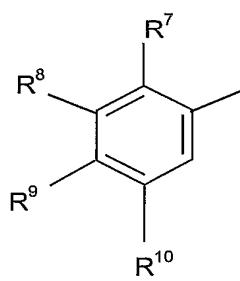
wherein represents either a single or a double bond,

5 R^2 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo, and C_{1-6} haloalkyl;
 R^3 is selected from hydrogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo, and C_{1-6} haloalkyl;

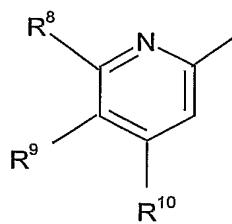
10 R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4, and

Ar is a group selected from

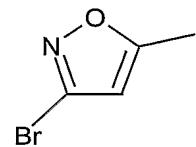
15



(e)



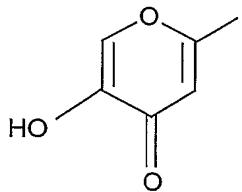
(f)



(g)

20

and



(h)

wherein R⁸ represents hydrogen, halogen, -(CH₂)_qOR¹¹, -NR¹¹C(O)R¹², -NR¹¹SO₂R¹², -SO₂NR¹¹R¹², -NR¹¹R¹², -OC(O)R¹³ or OC(O)NR¹¹R¹²,

5 and R⁷ represents hydrogen, halogen or C₁₋₄ alkyl;

or R⁸ represents -NHR¹⁴ and R⁷ and -NHR¹⁴ together form a 5- or 6- membered heterocyclic ring;

10 R⁹ represents hydrogen, halogen, -OR¹¹ or -NR¹¹R¹²;

R¹⁰ represents hydrogen, halogen, haloC₁₋₄ alkyl, -OR¹¹, -NR¹¹R¹², -OC(O)R¹³ or OC(O)NR¹¹R¹²;

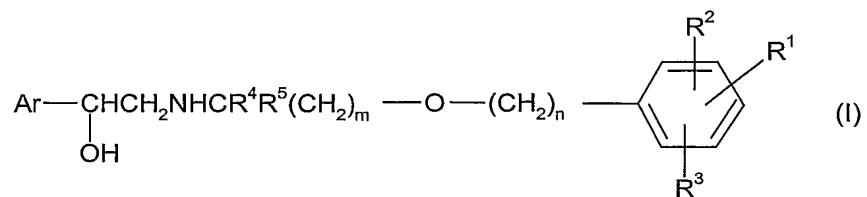
15 R¹¹ and R¹² each independently represents hydrogen or C₁₋₄ alkyl, or in the groups -NR¹¹R¹², -SO₂NR¹¹R¹² and -OC(O)NR¹¹R¹², R¹¹ and R¹² independently represent hydrogen or C₁₋₄ alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

20 R¹³ represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy or halo C₁₋₄ alkyl; and

q is zero or an integer from 1 to 4.

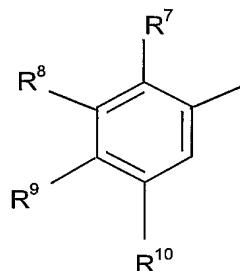
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2. A compound of formula (I)

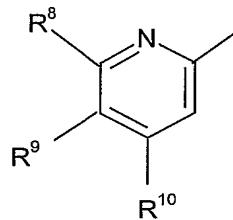


or a salt, solvate or physiologically functional derivative thereof,

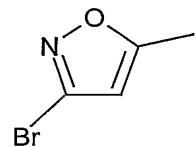
5 wherein m, n, R¹, R², R³, R⁴ and R⁵ are as defined in claim 1, and
 Ar represents a group selected from:



(e)

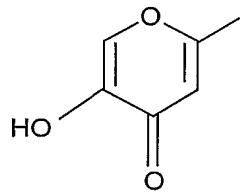


(f)



(g)

and



(h)

10 wherein R⁸ represents halogen, -(CH₂)_qOR¹¹, -NR¹¹C(O)R¹², -NR¹¹SO₂R¹²,
 -SO₂NR¹¹R¹², -NR¹¹R¹², -OC(O)R¹³ or OC(O)NR¹¹R¹²,
 and R⁷ represents hydrogen, or C₁₋₄ alkyl;
 or R⁸ represents -NHR¹⁴ and R⁷ and -NHR¹⁴ together form a 5- or 6- membered
 heterocyclic ring;

and R⁹, R¹⁰, R¹¹, R¹² and q are as defined in claim 1.

3. A compound of formula (I) according to claim 1 or claim 2 wherein, in a moiety selected from (a), (b), (c) and (d), --- represents a double bond.

5

4. A compound of formula (I) according to any of claims 1 to 3 wherein R² and R³ each represent hydrogen.

5. A compound of formula (I) according to any of claim 1 to 4 wherein R⁴ and R⁵ are

10 each independently selected from hydrogen and methyl.

6. A compound of formula (I) according to any of claims 1 to 5 wherein m is 3, 4, 5 or 6 and n is 3, 4, 5 and 6.

15 7. A compound of formula (I) according to any of claims 1 to 6, selected from:

1-[3-(4-[(2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl)phenyl]pyrimidine-2,4(1H,3H)-dione;

3-[3-(4-[(2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl)phenyl]dihydropyrimidine-2,4(1H,3H)-

20 dione;

5-[3-(4-[(2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl)phenyl]pyrimidine-2,4(1H,3H)-dione;

3-[3-(4-[(2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl)phenyl]pyrimidine-2,4(1H,3H)-dione;

25 5-[(1R)-2-[(6-[4-(4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenyl]butoxy]hexyl)amino]-1-hydroxyethyl]-2-hydroxyphenylformamide;

and salts, solvates and physiologically acceptable derivatives thereof.

30 8. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

9. A compound of formula (I) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

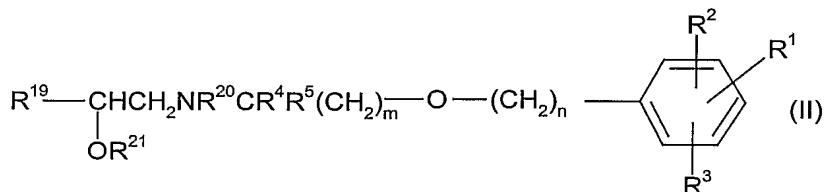
5 10. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

10 11. The use of a compound of formula (I) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated.

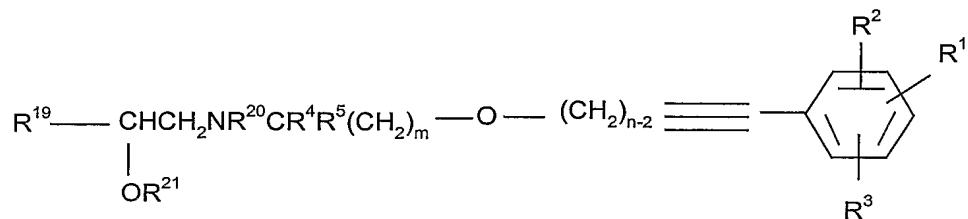
15 12. A process for the preparation of a compound of formula (I), according to any of claims 1 to 7, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

(a) deprotection of a protected intermediate, for example of formula (II).

20



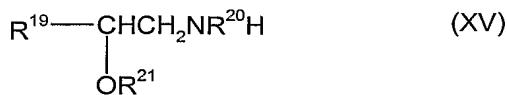
(b) reduction of a compound of formula (XIV):



(XIV)

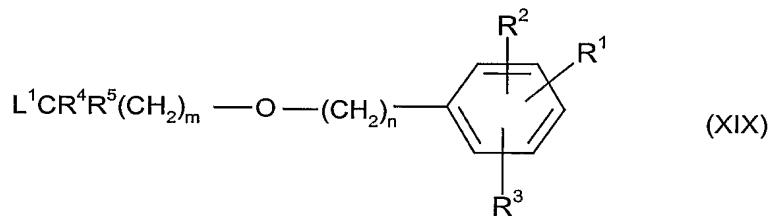
wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as defined for formula (I) and R^{19} , R^{20} , and R^{21} each independently represent a hydrogen atom or a protecting group as defined for formula (II).

5 (c) alkylation of an amine of formula (XV):



with a compound of formula (XIX):

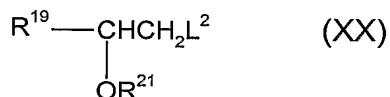
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wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) and L^1 is a leaving group as herein before defined for the compound of formula (VIII);

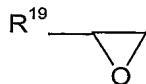
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(d) reacting a compound of formula (XX):



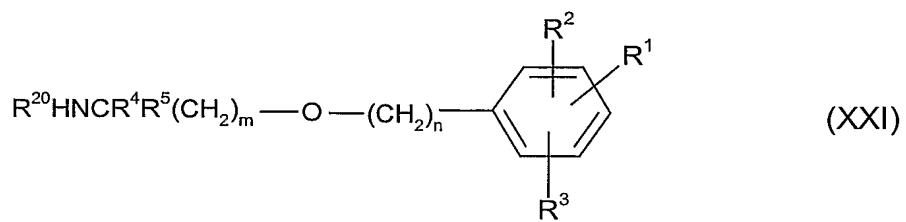
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wherein R^{19} and R^{21} are as hereinbefore defined and L^2 is a leaving group, or a compound of formula (XXa):



(XXa)

with an amine of formula (XXI):



5 followed by the following steps in any order:

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer from a mixture of enantiomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or isomeric functional derivative thereof.

10

13. A compound of formula (II), (III) or (IV) as defined hereinabove.

15

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INTERNATIONAL SEARCH REPORT

International Application No	PCT/EP 03/09992
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D239/54 C07D239/22 A61K31/513 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03/072539 A (BLAKE KEITH ; COE DIANE MARY (GB); GLAXO GROUP LTD (GB); PROCOPIOU PAN) 4 September 2003 (2003-09-04) page 78; examples i,ii -----	13
P, X	WO 03/024439 A (COE DIANE MARY ; GLAXO GROUP LTD (GB); BOX PHILIP CHARLES (GB); LOOKER) 27 March 2003 (2003-03-27) page 76; example 51 claim 1 -----	1-13
A	US 4 990 505 A (SKIDMORE IAN F ET AL) 5 February 1991 (1991-02-05) column 47; example 9 column 50; examples p,q column 51; example 13 claim 1 ----- -/-	1-13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

^o Special categories of cited documents :

- ^{*A*} document defining the general state of the art which is not considered to be of particular relevance
- ^{*E*} earlier document but published on or after the international filing date
- ^{*L*} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ^{*O*} document referring to an oral disclosure, use, exhibition or other means
- ^{*P*} document published prior to the international filing date but later than the priority date claimed

- ^{*T*} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- ^{*X*} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- ^{*Y*} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- ^{*&*} document member of the same patent family

Date of the actual completion of the international search

17 December 2003

Date of mailing of the international search report

30/12/2003

Name and mailing address of the ISA
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 Fax: (+31-70) 340-3016

Authorized officer

Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/09992

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/65877 A (GLAXO GROUP LTD ; DONALDSON KELLY HORNE (US); SHEARER BARRY GEORGE (US) 23 December 1999 (1999-12-23) claims -----	1-13
A	GB 2 230 523 A (GLAXO GROUP LTD) 24 October 1990 (1990-10-24) claims -----	1-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 13 is unclear (Art. 6 PCT) since it relates to compounds (II), (III), (IV) which are not defined in the claims (the definition of compounds (II) in claim 12 is not clear since there is no definition of R19). Compounds (II), (III) and (IV) have been searched taking the definitions on pages 21-25 of the description.

The claims are also directed to "physiologically functional derivatives" of structurally defined compounds. Since in the absence of any information about the metabolic pathway of the claimed class of compounds it is unclear (Art. 6 PCT) which structural terms should be covered by such a definition, a meaningful search in this respect is impossible. The search has been restricted to compounds structurally defined in the claims and esters thereof (cf. page 8 lines 19-23 of the description).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORTInterr application No.
PCT/EP 03/09992**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

 International Application No
 PCT/EP 03/09992

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03072539	A 04-09-2003	WO	03072539 A1	04-09-2003
WO 03024439	A 27-03-2003	WO	03024439 A1	27-03-2003
US 4990505	A 05-02-1991	AU AU BE CA CH DE DK ES ES FI FR GB GR IL IT JP LU NL NO NZ PT SE ZA CA	582573 B2 4134885 A 902213 A1 1252785 A1 667264 A5 3513885 A1 173785 A 8702880 A1 8800132 A1 851523 A 2562889 A1 2159151 A ,B 850936 A1 74940 A 1181642 B 61033147 A 85856 A1 8501124 A 851524 A ,B, 211822 A 80304 A ,B 8501895 A 8502851 A 1255666 A1	06-04-1989 24-10-1985 17-10-1985 18-04-1989 30-09-1988 17-10-1985 18-10-1985 01-04-1987 01-01-1988 18-10-1985 18-10-1985 27-11-1985 25-11-1985 30-06-1988 30-09-1987 17-02-1986 11-06-1986 18-11-1985 18-10-1985 29-11-1988 01-05-1985 18-10-1985 29-04-1987 13-06-1989
WO 9965877	A 23-12-1999	AU AU BR CA CN EA EE WO EP HR HU JP NO NZ PL SK TR US ZA	753004 B2 4510399 A 9911182 A 2334713 A1 1312800 T 3641 B1 200000744 A 9965877 A1 1087943 A1 20000854 A1 0102668 A2 2002518374 T 20006319 A 508805 A 344865 A1 19082000 A3 200100299 T2 6251925 B1 200007417 A	03-10-2002 05-01-2000 13-03-2001 23-12-1999 12-09-2001 28-08-2003 15-04-2002 23-12-1999 04-04-2001 31-12-2001 28-12-2001 25-06-2002 09-02-2001 29-08-2003 19-11-2001 11-09-2001 21-06-2001 26-06-2001 12-12-2001
GB 2230523	A 24-10-1990	NONE		